

## Prophylaxis and Treatment of Invasive Fungal Infections in Adult Haemato-oncology patients

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## SECTION 1: Background

Invasive fungal infections (IFI) including invasive candidiasis, aspergillus and mucormycosis can cause significant morbidity and mortality among patients with haematological malignancies and are associated with increased healthcare costs.

### Risk factors for IFIs include:

- Prolonged neutropenia during remission, induction, intensive chemotherapy, transplant conditioning and/or due to underlying disease
- Receipt of:
  - high and/or prolonged courses of steroids; T cell suppressors (e.g., calcineurin inhibitors); Monoclonal antibodies with T-cell depletion activity (e.g., alemtuzumab); anti-human thymocyte immunoglobulin (ATG); anti-TNF monoclonal antibodies (e.g., infliximab); TNF- $\alpha$  inhibitors (e.g., etanercept); purine analogues
- Iron overload
- Graft versus host disease (GvHD) in allogeneic stem cell transplant recipients
- Other comorbidities; CMV disease and respiratory viral infections, diabetes, respiratory disease (COPD, pulmonary fibrosis etc.), malnutrition.
- Environment factors; construction work, gardening, lack of laminar air flow

### Definitions of IFIs

Based on the EORTC/MSG consensus definition of Invasive fungal Infections, infections can be classified as “possible”, “probable,” and “proven” based on a range of host factors, clinical features and mycologic evidence (Appendix 1). Whilst these definition criteria have proven their value for clinical research, in clinical practice→ in clinical practice, treatment is often initiated for possible/probable infections. **The possibility of invasive fungal infection must be considered in patients with neutropenic fever, which is persistent despite broad spectrum antibiotic treatment. The diagnostic and treatment strategy in these patients should be discussed with the ID/Microbiology team.**

## SECTION 2: Risk stratification and recommended antifungal prophylaxis

The type of antifungal prophylaxis administered should reflect the risk of a patient developing an invasive fungal infection (IFI). Broadly speaking patients can be categorized into very high or high, low or very low risk of an IFI depending on patient, disease and treatment factors (intensity and expected length of neutropenia).

### 2.1. Very high/ High-risk patients

Very high/ High risk patients are defined as:

- History of a prior proven, probable, or possible invasive fungal infection and due to receive intensive chemotherapy, CAR-T therapy, or a stem cell transplant.
- Acute Lymphoblastic Leukaemia (ALL) patients receiving induction therapy.
- Acute myeloid leukaemia (including APML) or MDS receiving intensive chemotherapy, until recovery from neutropenia and complete remission.
- Chronic Myeloid Leukaemia (CML) receiving intensive chemotherapy
- Severe/very severe aplastic anaemia with prolonged neutropenia, neutrophil count  $< 1 \times 10^9/L$
- Aplastic anaemia patients receiving anti-human thymocyte immunoglobulin (ATG) therapy
- Allogeneic stem cell transplant recipients, during transplant

- Allogeneic stem cell transplant recipients with acute or chronic graft versus host disease (GvHD); steroid dependent/refractory, or grade 3 or 4
- Allogeneic stem cell transplant recipients receiving infliximab or systemic steroids > prednisolone 20mg per day (or equivalent) for treatment of GVHD. Prophylaxis should continue until the patient is on a prednisolone ≤ 20mg.
- Stem cell transplant recipients with prolonged secondary neutropenia (depth and duration as per above) due to graft failure or autoimmune complications.
- Autologous stem cell transplant recipients with history of previous Invasive Aspergillosis, expected prolonged neutropenia >2 weeks or prolonged neutropenia prior to time of transplant.

Prophylaxis should be prescribed for the duration of neutropenia until consistent count recovery (neutrophils >1 x 10<sup>9</sup>/L).

### A) First line mould active azole prophylaxis

**High risk patients** should receive **mould active** prophylaxis with posaconazole or voriconazole.

#### Posaconazole prophylaxis dosing

Oral route	Intravenous route
<p><b>Tablets:</b> Loading dose 300mg BD for 1<sup>st</sup> day, then 300mg OD thereafter. Tablets can be taken with or without food.</p> <p><b>Oral Suspension:</b> 200mg TDS. Taken with or immediately after food to enhance oral absorption.</p>	<p>Loading dose 300mg BD for 1<sup>st</sup> day, followed by 300mg OD <b>diluted</b> and given via intravenous infusion over 90 minutes via a central venous access*</p> <p>* If a central venous access device is unavailable, a <b>single infusion</b> can be given peripherally <b>diluted</b> through a large vein over 30 minutes</p>

#### Voriconazole prophylaxis dosing

Oral route	Intravenous route
<p><b>Tablet or suspension</b></p> <p><b>Body weight ≥40 kg:</b> loading dose 400 mg every 12 hours for 2 doses, then maintenance 200 mg BD</p> <p><b>Body weight &lt;40 kg:</b> loading dose 200 mg every 12 hours for 2 doses, then maintenance 100 mg BD</p>	<p>Loading dose 6mg/kg every 12 hours for 2 doses then maintenance 4mg/kg BD <b>diluted</b> and given via intravenous infusion at a maximum rate of 3 mg/kg per hour over 1 to 3 hours via a central line or large peripheral line.</p> <p>(If not tolerated, maintenance dose can be reduced to 3mg/kg BD).</p>

### B) Alternative non-azole prophylaxis

Where **azole prophylaxis is unsuitable**, treatment with an **echinocandin agent or AmBisome<sup>®</sup>** (liposomal amphotericin) should be considered in patients **with:**

- Significant adverse events with azoles (e.g., hepatotoxicity).
- Clinically significant drug interactions, unable to be managed by therapeutic drug monitoring and/or dose modifications
- **ALL Induction:** ALL patients receiving vinca alkaloids, as part of their induction chemotherapy schedule should receive prophylaxis with ONCE weekly AmBisome<sup>®</sup> (liposomal amphotericin)

**Micafungin** prophylaxis dosing**Body weight > 40kg:** micafungin 50mg ONCE daily via IV infusion over 1 hour**Body weight ≤ 40kg:** micafungin 1mg/kg/day via IV infusion over 1 hour**Caspofungin** dosing**Body weight > 80 kg:** 70mg IV on Day 1, then 70mg ONCE daily via IV infusion over 1 hour.**Body weight <80 kg:** 70mg IV on Day 1, then 50mg ONCE daily via IV infusion over 1 hour.**AmBisome® (liposomal amphotericin)** prophylaxis dosingAmBisome® (liposomal amphotericin) 7mg/kg **ONCE WEEKLY** via IV infusion over 2 hours.**Test dose:** An initial test dose of 1mg over 10 minutes should be given prior to the first dose of AmBisome® (liposomal amphotericin). The patient should be observed for at least 30 minutes for signs and symptoms of anaphylaxis. If no reaction occurs, the remainder of the dose can be administered safely, and no further test doses are required for subsequent doses.**Renal Impairment:** if there is concern about renal function, prophylactic doses of either AmBisome® (liposomal amphotericin) 3mg/kg three times a week OR 1mg/kg once daily maybe considered at consultant discretion with close monitoring of renal function.

## 2.2. Low risk patients

Low risk patients are defined as:

- Patients with Myeloid malignancy with neutropenia ( $<1 \times 10^9/L$ ) [if not in high-risk group]
- Lymphoma patients undergoing Intensive/dose escalated therapy.
- Autologous stem cell transplant recipients [if not in high-risk group]
- Fludarabine use in highly treatment-refractory patients with Chronic lymphocytic leukaemia (CLL) or low-grade lymphoma
- Alemtuzumab use, especially in highly treatment-refractory patients with CLL or lymphoma
- ALL CNS intensification/consolidation
- Patients with AML receiving consolidation chemotherapy
- Myeloma patients

### Antifungal prophylaxis for low-risk patients

- Patients in the low-risk group should receive prophylactic **oral fluconazole 50mg OD**.
- ALL patients receiving vinca alkaloids as part of their consolidation or intensification chemotherapy schedule should receive prophylaxis with weekly AmBisome® (liposomal amphotericin).

## 3.2. Very low risk patients

Very low risk patients are defined as:

- Lymphoma patients on standard therapy.
- Chronic Myeloid Leukaemia treated with TKIs or conventional treatment
- Other myeloproliferative malignancy
- Chronic lymphocytic leukaemia (CLL)
- Non-severe Aplastic Anaemia
- ALL patients on maintenance

**Primary antifungal prophylaxis is not routinely required** in these patients.

## SECTION 3: Diagnosis of Invasive Fungal Infections (IFIs)

### When to add antifungal treatment

Current approaches are empiric treatment (fever driven), or pre-emptive treatment (diagnostic driven) or a combination of the two depending on the availability of diagnostic tools.

### Diagnostic strategies

Neutropenic patients, with fever persisting at 96 hours despite broad spectrum antibiotic treatment:

- Obtain CT thorax (and sinuses where clinically indicated). Further scanning as clinically indicated.
- If radiological features are suggestive of invasive fungal disease, consider:
  - B-D-glucan on serum
  - Early bronchoscopy with BAL and commence empirical antifungal therapy. Samples should be sent for microscopy and culture, respiratory virus PCR, fungal microscopy and culture, PCP PCR, aspergillus antigen and fungi. Biopsies (lung, other tissue) should be sent for microscopy (incl Calcofluor) and culture, fungal microscopy and culture, and histology. Additional antigen and molecular studies (galactomannan, beta-D glucan and fungal PCR) should be discussed with the ID/micro team
  - Early discussion with chest medicine, ENT, radiology and infectious diseases/ microbiology as appropriate.
- In the absence of radiological features of invasive fungal infection, no empirical antifungal therapy is required and alternative causes for persisting fever should be sought. Consider repeat imaging after one week.

## SECTION 4: Empirical Treatment of Invasive Aspergillosis

### 4.1. Patients NOT on mould active prophylaxis

#### A) First line empiric treatment

All patients with suspected Invasive Aspergillosis, who are not on mould-active prophylaxis, should receive treatment with Intravenous voriconazole (oral voriconazole maybe appropriate in some selected clinically stable cases) except:

- If there is concern about possible mucormycosis (see below).
- Severe chronic liver disease (Child Pugh score C) – consider AmBisome® (liposomal amphotericin)
- Documented intolerance of voriconazole (e.g., significant ocular toxicity, neurotoxicity, visual/auditory hallucinations).

Patients who have responded to initial treatment with parenteral voriconazole can be switched to oral voriconazole only after therapeutic trough (pre-dose) levels have been achieved and there are no concerns about absorption and risk of therapeutic failure.

**Voriconazole** treatment dosing

Intravenous route	Oral route
Loading dose 6mg/kg every 12 hours for 2 doses then maintenance 4mg/kg BD <b>diluted</b> and given via intravenous infusion at a maximum rate of 3 mg/kg per hour over 1 to 3 hours via central line or a large peripheral line.  (If not tolerated, maintenance dose can be reduced to 3mg/kg BD).	<b>Tablet or suspension</b> <b>Body weight ≥40 kg:</b> loading dose 400 mg every 12 hours for 2 doses, then maintenance 200 mg BD  <b>Body weight &lt;40 kg:</b> loading dose 200 mg every 12 hours for 2 doses, then maintenance 100 mg BD

**B) Second line empiric treatment**

Decisions regarding selection of an agent other than Voriconazole for initial empiric antifungal therapy should be made based on clinical and patient specific grounds.

The choice of agent is at the discretion of the responsible consultant.

**AmBisome® (liposomal amphotericin) treatment dosing**

AmBisome® (liposomal amphotericin) 3mg/kg **once daily** initially (max 5mg/kg daily unless otherwise determined by Consultant Haematologist and ID/Microbiology consultant) via IV infusion over 2 hours.

**Test dose:** An initial test dose of 1mg over 10 minutes should be given prior to the first dose of AmBisome® (liposomal amphotericin). The patient should be observed for at least 30 minutes for signs and symptoms of anaphylaxis. If no reaction occurs, the remainder of the dose can be administered safely and no further test doses are required for subsequent doses.

**Isavuconazole (Microbiology Consultant recommendation ONLY)**

The following patients can be considered for IV (or oral) isavuconazole after discussion with Microbiology:

- Patients who have not responded to initial treatment which must include voriconazole if proven/probable IA; AmBisome® (liposomal amphotericin) is an option for treatment of invasive Aspergillosis prior to isavuconazole.
- Those who had significant adverse effects with voriconazole
- Where it has not been possible to achieve therapeutic drug levels with initial treatments.
- Initial treatment options are contraindicated e.g., Due to significant drug interactions (not manageable by therapeutic drug monitoring and/or dose alteration) or pre-existing co-morbidities (e.g., renal impairment with AmBisome® (liposomal amphotericin)).
  - Those with a positive culture for an organism covered by isavuconazole but not voriconazole.
- Liaise with Microbiology/ID for guidance on therapeutic drug monitoring.

**Isavuconazole treatment dosing - Completion of *Blueteq* is no longer required (August '22 onwards)**

Oral route	Intravenous route
Loading dose 200 mg TDS for 2 days then maintenance dose 200mg ONCE daily.	Loading dose 200 mg TDS for 2 days then maintenance dose 200mg ONCE daily via Intravenous Infusion over at least 1 hour through central line (administer using 0.2micron in line filter).  If central venous access device is unavailable, administer via a large peripheral vein and monitor for phlebitis

### C) Third line empiric treatment options

#### Caspofungin treatment dosing

**Body weight > 80 kg:** 70mg IV on Day 1, then 70mg ONCE daily via IV infusion over 1 hour.

**Body weight <80 kg:** 70mg IV on Day 1, then 50mg ONCE daily via IV infusion over 1 hour.

OR

#### Micafungin treatment dosing

**Body weight > 40 kg:** 100 mg ONCE daily via IV infusion over 1 hour (increased to 200 mg daily if inadequate response. Higher doses of 150mg to 300mg daily can be used)

**Body weight <40 kg:** 2 mg/kg IV ONCE daily via IV infusion over 1 hour (increased to 4 mg/kg daily if inadequate response)

#### 4.2. Patients ON mould active prophylaxis

Patients on mould-active prophylaxis who develop possible, probable or proven Invasive Aspergillosis should receive empiric treatment with either AmBisome® (liposomal amphotericin) OR micafungin OR caspofungin (treatment doses as above). The choice of agent is at the discretion of the responsible consultant.

### SECTION 5: Treatment of Mucormycosis

**Suspected and confirmed mucormycosis are emergencies** and require rapid action with surgical debridement (where indicated) and immediate treatment initiation.

If there is concern about possible mucormycosis then **AmBisome® (liposomal amphotericin)** should be used and the dose should be discussed with ID/microbiology (higher doses 5-10mg/kg per day are usually required for mucormycosis).

Isavuconazole is an alternative treatment option if AmBisome® (liposomal amphotericin) is contraindicated (e.g. renal impairment). Microbiology Consultant recommendation ONLY (see above for dosing).

### SECTION 6: Treatment of invasive candidaemia

#### First Line

An echinocandin (caspofungin or micafungin) is recommended as initial first line therapy for candidaemia

#### A) Third line empiric treatment options

#### Caspofungin treatment dosing

**Body weight > 80 kg:** 70mg IV on Day 1, then 70mg ONCE daily via IV infusion over 1 hour.

**Body weight <80 kg:** 70mg IV on Day 1, then 50mg ONCE daily via IV infusion over 1 hour.

OR

#### Micafungin treatment dosing

**Body weight > 40 kg:** 100 mg ONCE daily via IV infusion over 1 hour (increased to 200 mg daily if inadequate response. Higher doses of 150mg to 300mg daily can be used)

**Body weight <40 kg:** 2 mg/kg IV ONCE daily via IV infusion over 1 hour (increased to 4 mg/kg daily if inadequate response)

## Second line

AmBisome® (liposomal amphotericin) can be used as an alternative second line option.

### AmBisome® (liposomal amphotericin) treatment dosing

AmBisome® (liposomal amphotericin) 3mg/kg **once daily** initially (max 5mg/kg daily unless otherwise determined by Consultant Haematologist and ID/Microbiology consultant) via IV infusion over 60 minutes (For doses  $\geq 5$ mg/kg/day, intravenous infusion over a 2-hour period is recommended).

**Test dose:** An initial test dose of 1mg over 10 minutes should be given prior to the first dose of AmBisome® (liposomal amphotericin). The patient should be observed for at least 30 minutes for signs and symptoms of anaphylaxis. If no reaction occurs, the remainder of the dose can be administered safely, and no further test doses are required for subsequent doses.

## Alternative Treatment Option

In non-severe infections, if the patient is not ill and there is no prior azole exposure, treatment with fluconazole can be initiated for fluconazole-sensitive candida

### Fluconazole

Loading dose 800mg once daily on Day 1, then 400mg once daily Orally or Intravenously (must be intravenous in case of candidaemia)

### Management recommendations:

- Three sets of blood cultures should be sent to make the initial diagnosis
- Daily blood culture sets should be sent
- Ophthalmic review is advised
- Central venous catheter should be removed
- Treatment should continue until 14days after day if first negative blood cultures and resolution of symptoms attributable to candidemia.
- Switch from an echinocandin or AmBisome® (liposomal amphotericin) to oral fluconazole can be considered in stable patients within 5 to 7 days if the strain is sensitive. For candidaemia must have intravenous fluconazole for 14 days

## SECTION 7: Ongoing Management

### Stopping antifungal therapy

- The on-going administration of antifungal therapy should be subject to regular review.
- The diagnosis of invasive fungal infection is unlikely in the absence of radiological infiltrates or positive culture results.
- Antifungal therapy can be discontinued in patients with fever resolution, recovering neutrophils and no subsequent evidence of invasive fungal infection.

### Continuing anti-fungal therapy

- The on-going administration of antifungal therapy should be subject to regular review.
- Patients with evidence supporting a diagnosis of invasive fungal infection (imaging, histological, culture) should continue treatment. Modification to treatment may be made on the basis of culture, identification and sensitivities.



- Duration of treatment, particularly for invasive mould infections is difficult to precisely define. Treatment of proven or probable aspergillosis should continue until there is clear clinical improvement, accompanied by radiological response and improvement in immune status with an expectation that treatment will continue for a minimum of 6 weeks. Longer treatment durations may be appropriate and should be considered on an individual basis.

### Future prophylaxis

- Patients who have undergone treatment for invasive fungal (mould) infections are candidates for secondary prophylaxis if they are to undergo further therapy resulting in significant neutropenia or immunosuppression (see section for details).

## SECTION 8: Supportive Drug-Specific information and Therapeutic Drug Monitoring

### Voriconazole

- Voriconazole has the potential for a number of significant drug-drug interactions which may require alternative therapy, dose adjustments and/or TDM monitoring e.g. voriconazole increases ciclosporin and tacrolimus levels, also voriconazole levels maybe be reduced in patients receiving letermovir for CMV prophylaxis so it is particularly important to undertake TDM monitoring in patients receiving both drugs. Always check for drug interactions.
- Tablets are to be taken at least one hour before, or one hour after a meal.
- Oral suspension is to be taken at least one hour before, or two hours after a meal.

#### Voriconazole therapeutic drug monitoring:

- Target level for prophylaxis and treatment is 1-5mg/L: higher trough level >2mg/L is recommended for severe infections (Discuss with Microbiology/ID team). Levels >5mg/L are associated with increased toxicity particularly CNS toxicity and visual disturbances.
- Measurement of steady state trough pre-dose level is recommended 5-7 days after starting therapy. Subsequent monitoring to be done as clinically indicated, for example:
  - If patients receiving voriconazole treatment for IFIs, consider repeat level during second week of therapy, additional samples as clinically indicated to confirm level still in therapeutic range.
  - Suspected toxicity associated with high plasma concentrations.
  - Starting or stopping concurrent CYP450 enzyme inhibitors or inducers.
  - Concerns about poor gastrointestinal absorption (GvHD, diarrhea, mucositis) over prolonged period.
  - Change in dose, or route of administration, suspected poor adherence.
- **Dose adjustments**
  - Trough level <1mg/L: increase dose by 1mg/kg 12 hourly rounded to tablet size (50mg or 100mg). Recheck level after 7 days. Make sure the patient is taking the drug on an empty stomach.
  - Trough level 1-5mg/L: continue current dosing
  - Trough level >5mg/L: consider discontinuation and recommencement at lower dose
- **Visual disturbances** (including hallucinations) are reported in up to 30% of patients. These are transient and usually become less pronounced with repeated doses and do not necessarily require withdrawal of the drug.
- **Photosensitivity:** Voriconazole has been associated with phototoxicity reactions.
- **Squamous cell carcinoma** of the skin has also been reported in patients receiving voriconazole, some of whom have reported prior phototoxic reactions. All patients should be educated about avoiding exposure to direct sunlight during voriconazole treatment and using measures such as protective clothing and sufficient sunscreen with high sun protection factor (SPF).

- **Other side effects:** increase in transaminases and hepatic injury, hallucinations, psychosis, QT prolongation (electrolyte disturbances such as hypokalemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation or during IV voriconazole therapy, consider ECG monitoring as clinically indicated).
- **Renal impairment:** In patients receiving IV voriconazole who have renal impairment (CrCl <50 ml/min) accumulation of the vehicle SBEDC can occur, therefore renal function should be monitored closely. Consideration should be given to change to oral formulation if deemed clinically appropriate.
- **Hepatic Impairment:** in patients with Severe chronic liver disease (Child Pugh score C) – consider alternative therapy. In patients with moderate liver impairment (Child Pugh score B), consider reducing the maintenance dose of voriconazole by 50%.
- Duration of voriconazole therapy should not exceed 180 days (6 months).

### Posaconazole

- Posaconazole has the potential for a number of significant drug-drug interactions which may require alternative therapy, dose adjustments and/or TDM monitoring e.g. posaconazole increases ciclosporin and tacrolimus levels.

#### Oral

- Tablet form has better bioavailability and is preferred to oral suspension.
- The oral suspension should be taken with or immediately after food to enhance oral absorption.
- The tablet and oral suspension are **NOT to be used interchangeably** due to the differences between these two formulations in frequency of dosing, administration with food and plasma drug concentration achieved. Therefore, follow the specific dosage recommendations for each formulation.

#### Intravenous

- Consider intravenous formulation if oral route is unavailable or absorption may be impaired (e.g. severe mucositis)
- In patients receiving IV posaconazole who have renal impairment (CrCl <50 ml/min) accumulation of the vehicle SBEDC can occur, therefore renal function should be monitored closely. Consideration should be given to change to oral tablets if deemed clinically appropriate.

#### Therapeutic drug monitoring

- Routine TDM monitoring is not required for posaconazole prophylaxis, but can be considered in selected cases such as apparent clinical failure, concern due to malabsorption over prolonged period of time or if patient taking oral suspension. The recommended prophylaxis target level >0.7 mg/L with measurement of trough level 7 days after starting therapy.

### AmBisome® (liposomal amphotericin)

- **Test dose:** An initial test dose of 1mg over 10 minutes should be given prior to the first dose of AmBisome® (liposomal amphotericin). The patient should be observed for at least 30 minutes for signs and symptoms of anaphylaxis. If no reaction occurs, the remainder of the dose can be administered safely and no further test doses are required for subsequent doses. If a severe allergic or anaphylactic reaction occurs, the infusion should be immediately discontinued and the patient should not receive further infusion of AmBisome® (liposomal amphotericin).
- Consideration of precautionary measures for the prevention or treatment of infusion reactions should be given to patients who receive AmBisome® (liposomal amphotericin) therapy. Slower infusion rates or pre-medication with chlorphenamine and hydrocortisone can be considered.
- **Electrolyte derangement:** Due to the risk of hypokalaemia, and hypomagnesaemia, appropriate potassium and magnesium supplementation may be required during the course of AmBisome®

administration. For persistent hypokalaemia, consider commencing patients on amiloride 5 mg po daily. Monitor renal function and U & Es daily.

- **Renal impairment:** To reduce the risk of nephrotoxicity, ensure that patient is well hydrated and consider stopping other nephrotoxic drugs.
- **Safety Alert:** Serious harm and fatal overdoses have occurred following confusion between amphotericin products. Ensure that the correct medicine AmBisome® (liposomal amphotericin) is selected when prescribing on the electronic prescribing system, when dispensing and administering; verify the product name and dose before administration.

### Micafungin

- During administration of micafungin, anaphylactic/anaphylactoid reactions, including shock, may rarely occur. If these reactions occur, micafungin infusion should be discontinued and appropriate treatment administered.

## SECTION 9: Commonly encountered Azole Drug Interactions

**Azole antifungal agents are associated with a number of clinically significant drug interactions** that may necessitate alternative treatment, dose adjustments and/or therapeutic drug monitoring when starting/stopping each agent.

**Voriconazole** is *metabolised by cytochrome P450 isoenzymes*, CYP2C19, CYP2C9, and CYP3A4, it is also a **strong CYP3A4 inhibitor**.

**Posaconazole** is metabolised via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp), it is also a **strong inhibitor of CYP3A4**.

**Isavuconazole** is a substrate of CYP3A4 and CYP3A5, it is a **moderate inhibitor of CYP3A4/5**, a mild CYP2B6 inducer, and mild inhibitor of P-glycoprotein (P-gp).

The table below summarizes some of the commonly encountered drug interactions and recommendations from summary of product characteristics and Stockley's drug interactions. **This list is not conclusive;** always check for drug interactions when initiating/stopping new concurrent therapies. Discuss with pharmacist for advice.

Agent	Interaction	Recommendation concerning co-administration
<b>Chemotherapy agents</b>		
<b>Gemtuzumab Ozogomaicin</b>	Increased potential risk of hepatotoxicity	Azole antifungals should not be used until 5 days after the last dose of GO to reduce risk of hepatotoxicity
<b>Gilteritinib</b>	Azoles are predicted to increase gilteritinib exposure	Monitor for gilteritinib adverse effects, QT prolongation (perform ECG monitoring), and pancreatitis. Consider dose reduction.
<b>Midostaurin</b>	Azoles are predicted to increase exposure to midostaurin	Monitor for midostaurin adverse effects, QT prolongation, perform ECG monitoring
<b>Ruxolitinib</b>	Azoles predicted to increase the exposure to ruxolitinib	Recommendations depending on indication. In the setting of GvHD where lower ruxolitinib 10mg BD dose is used, no dose reduction of ruxolitinib is required unless in the context of toxicity.

<b>Venetoclax</b>	Azoles markedly increase the exposure to venetoclax and increase the risk of tumour lysis syndrome	Recommendations depending on indication, dose reduction of venetoclax dose by 75% if concurrent use is necessary. In the setting of CLL concurrent use is contraindicated during the titration phase. In the setting of AML receiving venetoclax plus azacitidine chemotherapy, as per the Cancer Drugs Fund, patients should receive posaconazole or voriconazole prophylaxis from Day 4 and throughout their treatment. The reason for this is that posaconazole will significantly increase venetoclax levels, allowing a much lower dose than usual of venetoclax (100mg rather than 400mg) to be used, increasing the cost-effectiveness of the schedule.
<b>Vinca Alkaloids</b>	Increased risk of neurotoxicity including peripheral neuropathy and seizures in combination with azoles	Concurrent use contraindicated. ALL patients receiving vinca alkaloids, as part of their induction chemotherapy schedule should receive prophylaxis with ONCE weekly AmBisome® (liposomal amphotericin).
<b>Busulfan</b>	Azoles may decrease busulfan clearance and increase risk of toxicity including risk of veno-occlusive disease	In the setting of HSCT conditioning, consider starting azole prophylaxis from day 0 once busulfan administration is complete
<b>Immunosuppressive agents</b>		
<b>Ciclosporin</b>	Posaconazole and voriconazole increase ciclosporin with an associated increased risk of nephrotoxicity	Reduce ciclosporin dose by 50% when initiating concurrent therapy with voriconazole or posaconazole with monitoring of ciclosporin levels.
<b>Tacrolimus</b>	Posaconazole and voriconazole greatly increase tacrolimus levels with an associated increased risk of nephrotoxicity  Potentially increase risk of QT prolongation with concurrent voriconazole	Tacrolimus dose should be initially reduced to one-third of the original dose when initiating concurrent therapy with voriconazole or posaconazole with monitoring of tacrolimus levels.
<b>Sirolimus</b>	Posaconazole and voriconazole greatly increase sirolimus concentrations AUC by up to 11 fold	Concurrent use of sirolimus with voriconazole is contraindicated, avoid concurrent use.  Avoid concurrent use with posaconazole. If it is essential, greatly reduce sirolimus dose (give one quarter to one third of the original dose); closely monitor sirolimus concentrations and effects (e.g. on renal function), adjusting the sirolimus dose as necessary.
<b>Mycophenolate mofetil</b>	Isavuconazole modestly increases mycophenolate exposure	monitoring for mycophenolic acid -related adverse effects (such as diarrhea,

		vomiting, and leucopenia) is advised
<p>Note: isavuconazole slightly increases ciclosporin and sirolimus levels and moderately increased tacrolimus levels. Generally the degree of interaction between isavuconazole and these immunosuppressive agents appears to be less than that reported for other triazole antifungal agents: the summary of product characteristics recommends monitoring of plasma levels and appropriate dose adjustment if required. Stockley's indicates that some recommendations suggest an initial tacrolimus dose reduction of 50%, followed by further reductions of 25 to 50% as guided by weekly monitoring. Discuss with consultant and pharmacist.</p>		
<b>Antimicrobials and Antivirals</b>		
<b>Letermovir</b>	Co-administration of letermovir with voriconazole (a CYP2C19 substrate) results in significantly decreased voriconazole plasma concentrations	TDM for voriconazole is recommended the first 2 weeks after initiating or stopping letermovir, as well as after changing route of administration of letermovir or immunosuppressant
<b>Rifampicin</b> (Strong CYP3A4/5 inducer)	Rifampicin very markedly reduces the exposure to voriconazole and isavuconazole.  Rifampicin may also decrease posaconazole plasma concentrations	The concomitant administration of isavuconazole and voriconazole with rifampicin is contraindicated. Discuss with Micro ID/treating consultant.  If concurrent use with posaconazole is unavoidable, monitor closely for efficacy and perform TDM monitoring.
<b>Rifabutin</b> (Strong CYP3A4/5 inducer)	Voriconazole increases the plasma concentration of rifabutin and increases the risk of toxicity. Rifabutin moderately reduces the plasma concentration of voriconazole.  Posaconazole increases the plasma concentration of rifabutin and increases the risk of toxicity. Rifabutin slightly reduces the plasma concentration of posaconazole.  Rifabutin is predicted to decrease isavuconazole exposure.	Avoid Concurrent use with voriconazole unless benefits outweigh risks. Increase the oral voriconazole dose to 350 mg twice daily (200 mg twice daily in patients under 40 kg) and the intravenous dose to 5 mg/kg twice daily. Be alert for rifabutin toxicity (e.g. uveitis).  Avoid concurrent use with posaconazole unless the benefits outweigh the risks Monitor for reduced antifungal activity, perform TDM, increasing the posaconazole dose as necessary. Be alert for rifabutin toxicity (in particular uveitis).  Avoid concurrent use. If both drugs are given, monitor for isavuconazole efficacy and increase the dose if necessary. Discuss with Micro ID
<b>Erythromycin/Clarithromycin</b>	Erythromycin and clarithromycin are predicted to increase the exposure to posaconazole and isavuconazole  concurrent use of erythromycin/clarithromycin might increase the risk of QT prolongation	Monitor for adverse events
<b>Herbal and food interactions</b>		
<b>St John's Wort</b> (Strong CYP3A4/5 inducer)	St John's wort is predicted to decrease isavuconazole exposure. It also reduced voriconazole exposure by more than half.	Avoid concurrent use with voriconazole and isavuconazole. The voriconazole dose may need to be increased, at least initially with TDM monitoring.
<b>Food</b>	Food delays and reduces the oral	Voriconazole should be taken at least 1

	<p>absorption of voriconazole</p> <p>Posaconazole oral absorption is increased by food and nutritional supplements. The use of carbonated drinks, such as cola, improves posaconazole bioavailability from oral suspension.</p>	<p>hour before, or at least 1 to 2 hours after, a meal.</p> <p>Posaconazole oral suspension should be taken with food or a nutritional supplement.</p>
<b>Other</b>		
<b>Proton Pump inhibitor and H2 antagonists</b>	<p>Reduce the exposure to posaconazole oral suspension, but not to posaconazole gastro-resistant tablets</p>	<p>Avoid concurrent use where possible.                  Consider TDM monitoring</p>

**Audit**

1. Annual audit of all patients with positive fungal cultures.
2. Antifungal usage drug reports available from the pharmacy department.

**References**

Maertens JA1, et al. ECIL guidelines. European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. J Antimicrob Chemother. 2018 Dec 1; 73(12):3221-3230. Available online. <https://www.ncbi.nlm.nih.gov/pubmed/30085172>.

Frederic Tissot et al. ECIL-6 Guidelines For The Treatment Of Invasive Candidiasis, Aspergillosis and Mucormycosis In Leukaemia And Hematopoietic Stem Cell Transplant Patients. Haematologica March 2017 102: 433-444. Available online: <https://doi.org/10.3324/haematol.2016.152900>

Cornelly O et al. Global guideline for the diagnosis and management of mucormycosis. Lancet Infect Dis 2019; Nov 4<sup>th</sup>. Available online: [https://doi.org/10.1016/S1473-3099\(19\)30312-3](https://doi.org/10.1016/S1473-3099(19)30312-3)

Ullman et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018 May;24 Suppl 1:e1-e38.

Thomas F. Patterson et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases: 2016;63(4):e1–60

Peter G. Pappas et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases: 2016;62(4):e1–50

H. Ruth Ashbee et al. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother 2014; 69: 1162 –1176

Russel Lewis et al. ECIL-6 Guidelines. Triazole antifungal therapeutic drug monitoring. ECIL6 Meeting. September 11-12 2015. Available online. <http://www.ecil-leukaemia.com/telechargements2015/ECIL6-Triazole-TDM-07-12-2015-Lewis-R-et-al.pdf>

Andreas H. Groll ET AL. Pharmacokinetic Assessment of Drug-Drug Interactions of Isavuconazole With the Immunosuppressants Cyclosporine, Mycophenolic Acid, Prednisolone, Sirolimus, and Tacrolimus in Healthy Adults. Clin Pharmacol Drug Dev. 2017 Jan-Feb; 6(1): 76–85.

Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis. 2020; 71:1367-1376. Available online: <https://doi.org/10.1093/cid/ciz1008>

**Document review**

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<b>Name</b>	<b>Revision</b>	<b>Date</b>	<b>Version</b>	<b>Review date</b>
Dr Jean O'Driscoll, Microbiology Consultant, Dr Monique Andersson, Infection Consultant, On behalf of Thames Valley Microbiology Professional Development Group Claire Brandish (Pharmacist), Royal Berkshire Hospital Kate Russell-Hobbs (Pharmacist), Royal Berkshire Hospital Dr Rob Danby, Consultant Haematologist. Oxford University Hospital NHS Foundation Trust Nadjoua Maouche, Lead Haematology Pharmacist. Oxford University Hospitals NHS Foundation Trust	New document	March 2021	3.0	March 2023
Donna Constantine, Advanced Cancer Pharmacist, Oxford University Hospital NHS Foundation Trust	Update to remove Blueteq requirement for isavuconazole following NHSE HCD list update.	November 2022	3.1	March 2023



**Appendix 1: Revised EORTC/MSG Definitions of Invasive Fungal Infection, except for endemic mycoses**

**Possible:** 1 host factor + clinical criterion

**Probable:** 1 host factor + clinical criterion + mycological criterion

**Proven:** Positive microscopic analysis (by histopathologic, cytopathogenic or direct microscopic examination) of a specimen from a sterile site or positive culture from a sterile specimen/blood or positive cryptococcal antigen in the CSF

**Host factors:**

- Recent history of neutropenia  $<0.5 \times 10^9$  neutrophils/L (for  $>10$  days) temporally related to the onset of invasive fungal disease
- Hematologic malignancy ( active malignancy , in receipt of treatment or in remission in the recent past) such as acute leukaemia, lymphoma, multiple myeloma)
- Receipt of an allogeneic stem cell transplant
- Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of  $\geq 0.3$  mg/kg/day of prednisone equivalent for  $\geq 3$  weeks in the past 60 days
- Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF- $\alpha$  blockers, lymphocyte-specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days
- Treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, eg, ibrutinib
- Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency).
- Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids

**Clinical criteria**

Pulmonary Aspergillosis

The presence of 1 of the following 4 patterns on CT:

- Dense, well-circumscribed lesions(s) with or without a halo sign
- Air-crescent sign
- Cavity
- Wedge-shaped and segmental or lobar consolidation

Other pulmonary mould diseases

- As for pulmonary aspergillosis but also including a reverse halo sign

Tracheobronchitis

Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis

Sinonasal disease

Imaging showing sinusitis plus at least 1 of the following 3 signs:

- Acute localized pain (including pain radiating to the eye)
- Nasal ulcer with black eschar
- Extension from the paranasal sinus across bony barriers, including into the orbit

Central Nervous System infection

1 of the following 2 signs:

- Focal lesions on imaging
- Meningeal enhancement on MRI or CT

Disseminated candidiasis

At least 1 of the following 2 entities after an episode of candidaemia within the previous 2 weeks:

- Small, target-like abscesses in liver or spleen (bull's-eye lesions)
- Progressive retinal exudates on ophthalmologic examination

**Mycological criteria**

Direct test (cytology, direct microscopy, or culture).

Mould identified from sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by 1 of the following:

- Presence of fungal elements on microscopy indicating a mould
- Recovery by culture of a mould (e.g., *Aspergillus* sp., *Fusarium* sp., Mucorales, or *Scedosporium* spp.)

Indirect tests (detection of antigen or cell-wall constituents)

Aspergillosis only:

Galactomannan antigen

Antigen detected in plasma, serum, bronchoalveolar lavage fluid, or CSF .

Any 1 of the following:

Single serum or plasma  $\geq 0.7$  and BAL fluid  $\geq 0.8$

CSF  $\geq 1.0$

Aspergillus PCR

Any 1 of the following:

Plasma, serum or whole blood 2 or more consecutive PCR tests positive

BAL fluid 2 or more duplicate PCR tests positive

At least 1 PCR test positive in plasma, serum or whole blood and 1 PCR test positive in BAL fluid

Invasive fungal disease other than cryptococcosis and mucormycosis:

$\beta$ -D-glucan detected in serum.